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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,510	09/29/2005	Karoly Tihanyi	23394	6075

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K.F. ROSS P.C.
5683 RIVERDALE AVENUE
SUITE 203 BOX 900
BRONX, NY 10471-0900

EXAMINER	
SIMMONS, CHRIS E	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,510	TIHANYI ET AL.	
	Examiner	Art Unit	
	CHRIS E. SIMMONS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Abstract

The abstract of the disclosure is objected to because it does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mayer et al. (USP 5,840,731).

Applicant argues, at page 11 of the response, that tolperisone or eperisone is not equivalent since none of the muscle relaxers disclosed in the reference has a structure even remotely similar to same. Applicant further argues that the modes of action of centrally acting muscle relaxers can be different. This is not found to be persuasive because, despite, any alleged differences in structure and modes of action between muscle relaxers, the effect of relaxation of muscle is the same between muscle relaxants. Moreover, baclofen[1] - one of the muscle relaxers disclosed in the reference - and tolperisone[2], as well as eperisone, are known to block Ca channels in the CNS.

Applicant argues, at page 12, that the reference composition contains agents that are not currently claimed since the limiting words "consisting essentially of" are recited in the current claims. Applicant concludes that, consequently, the reference compositions are different from applicant's in 2 ways: 1) the muscle relaxants between the reference and the current invention are different and the reference requires additional active ingredients that are excluded from the claimed composition. The

[1] Wojcik et al. (Neuropharmacology. 1990 Oct;29(10):969-72). - discloses that Baclofen inhibits with high affinity an L-type-like voltage-dependent calcium channel in cerebellar granule cell cultures (title).

examiner does not find applicant's arguments to be persuasive because the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *MPEP § 2111.03[R3].* It is submitted that the muscle relaxant-containing compositions of the reference are completely suitable as anti-spasmodic and analgesic compositions. The basic and novel characteristics of the invention are not compromised by the addition of the analgesic agents disclosed in the reference. Accordingly, the claims that are limited by the phrase "consisting essentially of" do not preclude the analgesics of the reference from being present in the composition. And since there is no clear and concise description of the basic and novel characteristics of the current invention, the phrase "consisting essentially of" reads on the broader open-language of "comprising" when given its broadest reasonable interpretation.

It appears, at page 13, that applicant is making the argument that even though the reference discloses that pain due to muscle spasms can be treated with tolperisone, it does not necessarily mean that tolperisone can be considered an analgesic. Applicant also states that "muscle relaxant drugs are only useful in relieving pain associated with spasticity". The examiner believes that this statement would then support the notion that muscle relaxants *are* analgesics. The definition of an analgesic, according to the National Institute of General Medical Science (http://publications.nigms.nih.gov/medbydesign/glossary.html), is *'a medicine's ability to relieve pain, or a drug that alleviates pain'.* There is no requirement of a specific

[2] Kocsis et al. (J Pharmacol Exp Ther. 2005 Dec;315(3):1237-46. Epub 2005 Aug 26). - disclosing that

mechanism by which analgesia is achieved. Since an analgesic is a compound that relieves pain and muscle relaxants are used to relieve pain, then the muscle relaxant is also an analgesic.

Applicant has pointed to the disclosure of Weinbroum to illustrate that dextromethophan (DEX) is ineffective in treating chronic pain. Notwithstanding this disclosure the reference concludes at page 594: "Animal and clinical research indicate a beneficial role of NMDA receptor antagonists as part of *multi-modal* analgesic therapy, mainly for acute pain. For these patients, oral DM at doses of 30–90 mg appears to have an advantage over other antagonists in reducing the sensation of pain and sparing the requirement of conjointly administered analgesics, and has proven to have no or a low rate of untoward side effects. Further clinical trials, some currently now underway by the present authors, are still necessary to determine (1) the role of DM in various clinical pain-associated conditions, (2) the optimal clinical dose regimen that will considerably lower the rate of side effects, and (3) how long efficacious and safe treatment can be carried out both in acute *and chronic* pain syndromes". *Emphasis added.* Accordingly, DEX is still disclosed as effective to treat pain in a composition containing other pain relievers.

Applicant argues that the synergistic aspects of the combination of tolperisone or eperisone with DEX in the treatment of spasticity have been overlooked by the examiner. Applicant asserts that the synergistic results can be found in Tables 2 to 5 of the current specification. The examiner does not believe a proper showing of

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tolperisone-type drugs inhibit spinal reflexes via blockade of voltage gated sodium and calcium channels

synergistic results exists in Tables 4 and 5. In Table 5, there is no data that shows the inhibitory/anti-spasmodic results for DEX alone. Table 4 does not show results for tolperisone or eperisone. Accordingly, one cannot conclude from the disclosure that the results are more than additive for the combination of tolperisone or eperisone with DEX. However, the examiner does believe that Tables 2 and 3 constitute proper showings of synergism. However, the examiner does not find the synergism to be unexpected because tolperisone is expected to inhibit metabolism of dextromethorphan (see next obviousness rejection below). Even if the synergistic results are unexpected, *in arguendo*, the specification has only illustrated synergism between tolperisone (not eperisone) and DEX, where DEX is in the amount of 10 mg/kg and tolperisone is at 40 or 60 mg/kg and administered intraperitoneally. The declaration filed 12/05/0008, has only shown synergism between tolperisone (not eperisone) and DEX, where DEX is at a concentration of 0.25 micromolars and tolperisone is at 25 or 50 micromolars. Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." *MPEP § 716.02(d)R2.* In this case, the claims do not appear to be commensurate in scope with the showing of unexpected results for anti-spasticity combination of tolperisone and DEX. Claim 12, for example, does not recite a particular amount for the inert carrier; therefore, the total concentration of the tolperisone and dextromethorphan cannot be determined and would render the claim to not be commensurate in scope

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(title).

with the synergistic showings of record. Another example, is the administrative form is not recited in the claims. Synergism was demonstrated in Tables 2 and 3 when the compositions were administered intraperitoneally.

As for Table 6, it does not appear that the data represents a more than additive amount of the anti-allodynic effect demonstrated by combining tolperisone and DEX. For example, at 10 minutes, DEX showed a mean threshold of 7.57 g and tolperisone showed a mean threshold of 14.89 g. When the drugs are combined, the threshold increased to 19.71 g. Accordingly, applicant's arguments with regard to synergistic anti-allodynic effect of the invention are not found to be persuasive.

Applicant asserts, at page 17, that Table 3 shows unexpected results for the anti-spasmodic effect as well as the analgesic effect. The examiner, however, does not see any data with regard to analgesia in Table 3.

Claims 12-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 6,194,000 in view of USP 5,863,927, the combination taken further in view WO/2002/088100 (US 2004/0186136 is the US national phase and used herein to translate).

US '000 discloses a method for the therapeutic treatment of pain related to wind up in a human or animal. The method of the invention is practiced by administering to the subject an effective amount of an analgesic pharmaceutical composition which includes a NMDA receptor antagonist in an immediate release form combined with an

NMDA receptor antagonist in a sustained release form. The immediate release form and sustained release form are present in sufficient amounts to diminish or abolish wind up pain (abstract). Preferably the NMDA receptor antagonist is dextromethorphan or a pharmaceutically acceptable salt thereof. Studies indicate that activation of the NMDA receptor complex in the spinal dorsal horn leads to increased spontaneous neural discharge, expanded receptive fields and exaggerated responses to afferent input. These neural mechanisms may be expressed physically as hyperalgesia (increased pain sensation) and allodynia (pain arising from a stimulus that is not normally painful. The composition of the invention is suitable for the treatment of chronic or acute pain, for example to be administered pre-operatively. The composition of the invention may be in a form suitable for oral or rectal administration or for administration by transdermal, intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means. The reference does not expressly teach tolperisone.

US '927 discloses that, when used in therapeutic applications, dextromethorphan disappears rapidly from the bloodstream of most individuals. Dextromethorphan is broken down in the liver into several metabolites. Dextromethorphan can be oxidized by O-demethylation, in which one of the methyl groups is removed and two metabolites, dextrorphan and 3-methoxymorphinan, are produced. If the second methyl group is removed, the resulting metabolite is 5-hydroxymorphinan. Dextrorphan is known to have many of the biological activities of dextromethorphan. However, dextrorphan and 5-hydroxymorphinan become covalently bonded to other compounds in the liver, primarily

glucuronic acid or sulfur-containing compounds such as glutathione to form glucuronide or sulfate conjugates, which can not readily cross the blood-brain barrier and which are quickly eliminated from the body in the urine. The particular enzyme primarily responsible for dextromethorphan oxidation is debrisoquin hydroxylase, also known as, inter alia, cytochrome P-450 2D6 (i.e., CYP2D6). It discloses the use of inhibitors capable of inhibiting the oxidation of dextromethorphan by the liver enzyme debrisoquin hydroxylase. The invention describes dextromethorphan dosages in the range of about 20 mg/day to about 200 mg/day, preferably in the range of 20 to 150 mg/day, depending on factors such as the weight of the patient, the severity of the disorder, and the potency and dosage of the antioxidant agent used in conjunction with dextromethorphan. Dosages of other antioxidants will vary with the antioxidant, and should be determined on an individual basis. The reference does not expressly teach tolperisone.

US '136 discloses that tolperisone, a known analgesic, is metabolized by the CYP2d6 enzyme. The reference does not expressly teach

It would have been obvious to add tolperisone to the composition containing dextromethorphan. The motivation would have been to use the tolperisone to competitively inhibit metabolic oxidative demethylation of the dextromethorphan due to the tolperisone competing with dextromethorphan for the metabolic activity of the CYP2d6 enzyme. By doing so one would reasonably expect higher levels of

dextromethorphan to remain in the body for a longer period of time to treat diseases such as pain that is already known to be treatable by dextromethorphan. Since, it is known that dextromethorphan metabolites are conjugated and rendered incapable of crossing the BBB and are rapidly eliminated from the body, it would be motivational to inhibit metabolism and extend the time of dextromethorphan in the body so more of it can cross the BBB[3] and demonstrate its analgesic effects at the CNS level by antagonizing the activation of the NMDA receptor which leads to allodynia and hyperalgesia.

As for the amounts claimed, the concentrations and ratios claimed overlaps those disclosed in the reference and is, therefore, *prima facie* obvious. See MPEP § 2144.05 [R5]. Additionally, it would have been obvious to optimize the amounts by adding more tolperisone than dextromethorphan in order to saturate more of the CYP2D6 enzyme so there is fewer enzyme available to metabolize dextromethorphan. Finally, one of ordinary skill in the art would optimize the amounts "depending on factors such as the weight of the patient, the severity of the disorder, and the potency and dosage of the antioxidant agent used in conjunction with dextromethorphan" as stated in the '927 patent.

Conclusion

No claims are allowable at this time.

[3] USP 5,206,248 - discloses that dextromethorphan is an opioid that crosses the BBB.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. E. S./
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612